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NUMBER 4

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THE HUMAN BRAIN EVOLVING:

Paleoneurological Studies in Honor of Ralph L. Holloway

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FRONT COVER CAPTIONS

Center: Portrait of Ralph L. Holloway.
Upper left: A modern human brain.
Upper right: Ralph measuring landmarks on an endocast ca. 1976.
Lower right: Homo habilis cranium KNM-ER-1813 from Koobi Fora, Kenya (photo by Holloway).
Lower left: Ralph with an endocast of the Flores "hobbit" cranium.

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CHAPTER 11

Structural and Diffusion MRI of a Gorilla Brain Performed *Ex Vivo* at 9.4 Tesla

Jason A. Kaufman, J. Michael Tyszka, Francine "Penny" Patterson, Joseph M. Erwin, Patrick R. Hof, John M. Allman

Abstract

Data on brain connectivity in great apes are difficult to obtain because of the lack of reliable *ex vivo* chemical tracers and the preclusion of terminal experimentation using *in vivo* tracers. A new method for obtaining connectivity data, called diffusion-weighted MRI, is a variant of conventional MRI that allows researchers to measure the coherence and orientation of fiber tracts within an entire brain. From these imaging data, tract-tracing algorithms have been developed to conduct non-invasive tractography. Here we apply high-field diffusion-weighted MRI and probabilistic tractography on an isolated, fixed gorilla brain. To test the reliability of this method, we attempt to reconstruct two well-known fiber pathways: the visual (retino-geniculo-striate) pathway, and the corticospinal pathway. The results produced excellent reproductions of these pathways, but also included "false-positive" pathways caused by "tract-jumping" among adjacent fiber pathways. We conclude that diffusion-weighted MRI constitutes an important new tool for studying brain connectivity in humans and great apes, but researchers must be vigilant for false-positive pathways.

Introduction

> "To say that the white matter is but a uniform substance like wax in which there is no hidden contrivance, would be too low an opinion of nature's finest masterpiece. We are assured that wherever in the body there are fibers, they everywhere adopt a certain arrangement among themselves, created more or less according to the functions for which they are intended…all the diversity of our sensation and our movements depends upon this."
>
> -Nicolaus Steno (1671)

The heterogeneity of the brain's white matter was apparent even to 17th century anatomists whose dissections of large-scale fiber bundles were painstakingly described and illustrated [for a comprehensive review see (Schmahmann and Pandya, 2006)]. But the functional significance of these pathways remained largely mysterious until the development of methods for localizing particular functions to particular regions of the brain. White matter connectivity between functional regions was inferred first from lesion/degeneration studies (e.g., Damasio and Damasio, 1989; Goldman et al., 1971; Pribram and Mishkin, 1955) and later from chemical neuronal tracers (e.g., Barbas and Pandya, 1987; Van Essen et al., 1986). However, the terminal nature of these experiments restricts their application to laboratory animals and precludes their use in humans or apes. For this reason there has been an absence of comparative data on structural brain connectivity for humans and our ape relatives–data that could contain important phylogenetic signals on the evolution of the brain's wiring scheme.

Diffusion-weighted magnetic resonance imaging (DW-MRI) provides a new means for obtaining quantitative data on white matter connectivity. DW-MRI is sensitive to the magnitude and spatial orientation of Brownian water diffusion in tissue, which occurs more readily along axon tracts than across them (Basser et al., 1994; LeBihan et al., 2001). The method is non-invasive, and has been used successfully to trace known fiber pathways in laboratory animals and in humans (Basser et al., 2000; Conturo et al,. 1999; Mori et al., 1999; Xue et

al., 1999), and to quantify the coherence of white matter fiber tracts in healthy and diseased individuals (Barnea-Goraly et al., 2004; Michael, 2002; Moseley et al., 2002; Neil et al., 2002; Nguyen et al., 2005; Ramnani et al., 2004; Sundgren et al., 2004). Technical advances in DW-MRI have significantly improved the angular resolution of diffusion scanning (Jones et al., 1999), and an analytical method has been developed to characterize the uncertainty associated with DW-MRI tract-tracing (Behrens et al., 2003b). This process, called probabilistic tractography, has also recently been expanded to model crossing-fibers within voxels (Behrens et al., 2007).

Our purpose here is to demonstrate the feasibility of conducting DW-MRI tractography on an isolated, fixed brain using a high-field experimental imaging system. Fixed tissue is entirely compatible with DW-MRI, and there are distinct advantages for imaging *ex vivo* as opposed to *in vivo*: fixed tissue allows for extended scanning periods which substantially boosts the signal-to-noise ratio; and fixed tissue can be processed histologically following scanning. (Obviously, functional imaging (fMRI) is not possible *ex vivo*.) In this chapter, we present results from an *ex vivo* structural–(i.e., grey-white contrast) and diffusion–MRI experiment on a gorilla brain conducted on a 9.4 Tesla MRI system. To test the reliability of the probabilistic tractography method, we attempt to reconstruct two well-understood white matter pathways: the visual (retino-geniculo-striate) pathway and the motor (corticospinal) pathway.

Methods

The brain is that of an adult male gorilla, named Michael, who at the age of 27 succumbed to a myocardial disease characterized by deterioration of the heart's electrical conduction pathway. It is particularly important to note that careful prior preparations were made for quick and precise extraction of the brain with a minimal post-mortem interval. This type of preparation yields especially good tissue preservation, and should serve as a model for the compassionate use of tissue from great apes who have died from natural causes.

Within four hours post-mortem the brain was immersion fixed in 4% paraformaldehyde (freshly depolymerized) and subsequently stored in phosphate-buffered-saline with 0.01% sodium azide added as a preservative.

An acrylic canister was constructed so that the brain could be submerged in a high-viscosity perfluoropolyether (Galden, Solvay Solexis) that has a zero MR signal. The zero MR signal yields images of the brain in "black" or "empty" space, thereby aiding in subsequent tissue segmentation. The brain was wrapped in thin Teflon® (DuPont) which, as a fluorinated polymer, also has a zero MR signal, and positioned in the canister using sponges. The canister fits snugly inside a 180mm birdcage RF coil in our 9.4 Tesla Bruker imaging system (Bruker Biospin Ltd.).

Two series of scans were performed. The first was a high-resolution 3D FLASH sequence, lasting approximately 16 hours, with an anatomical resolution of 250 microns isotropic. The second series were high-angular-resolution diffusion scans (PGHE) weighted isotropically along 72 directions. A series of 6 diffusion scans, lasting approximately 36 hours in total, were averaged together in order to boost the signal-to-noise ratio, with a final resolution of 1mm isotropic.

All post-processing of the images were performed using Amira (Mercury, San Diego) and the FSL suite of MRI applications (Smith et al., 2004). For the diffusion imaging, post-processing steps included corrections for eddy-current distortions, followed by a computation termed Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (known as a BEDPOST operation). This computation involves a Markov Chain Monte Carlo resampling technique to construct probability distributions for diffusion parameters within each voxel (Behrens et al., 2003b). The BEDPOST operation requires complex computations for every voxel within the brain, and the computing time can be substantial: in this case it took approximately two weeks of computing time on a high-end Linux workstation to complete the BEDPOST operation. For each tractography trial, 10,000 samples were drawn from the global probability density function for each voxel in the seed mask.

Probabilistic tractography of the retino-geniculo-striate pathway was performed using the method of Behrens et al. (Behrens et al., 2003a). Specifically, seeds were placed at the grey-white border surrounding the lateral geniculate nucleus (LGN). This single-mask approach should identify projections both in the anterior direction (afferent fibers from the retina) and posterior direction (efferent fibers to the striate cortex).

Tractography of the corticospinal tract was performed using the method of Ciccarelli et al. (Ciccarelli et al., 2006). First, the neocortex is segmented and the boundaries of primary motor cortex are defined both morphologically (the posterior bank of the precentral gyrus) and histologically by the presence of Betz cells in Nissl-stained coronal sections. The M1 region-of-interest is then mapped into MRI space using an affine registration algorithm (Jenkinson and Smith, 2001). Next, a connectivity-based seed classification is performed on an axial mask through the internal capsule. This step identifies voxels within the posterior limb of the internal capsule mask that are most-likely to connect with primary motor cortex. Probabilistic tractography is then performed from the motor cortex seed mask, with the condition that only projections passing through the internal capsule mask are retained. In other words, the region of the internal capsule most likely to connect with primary motor cortex is defined as a waypoint mask for reconstructing the corticospinal tract. We also performed trials in which the medullary pyramids were masked as waypoints to further constrain the fibers to the corticospinal tract.

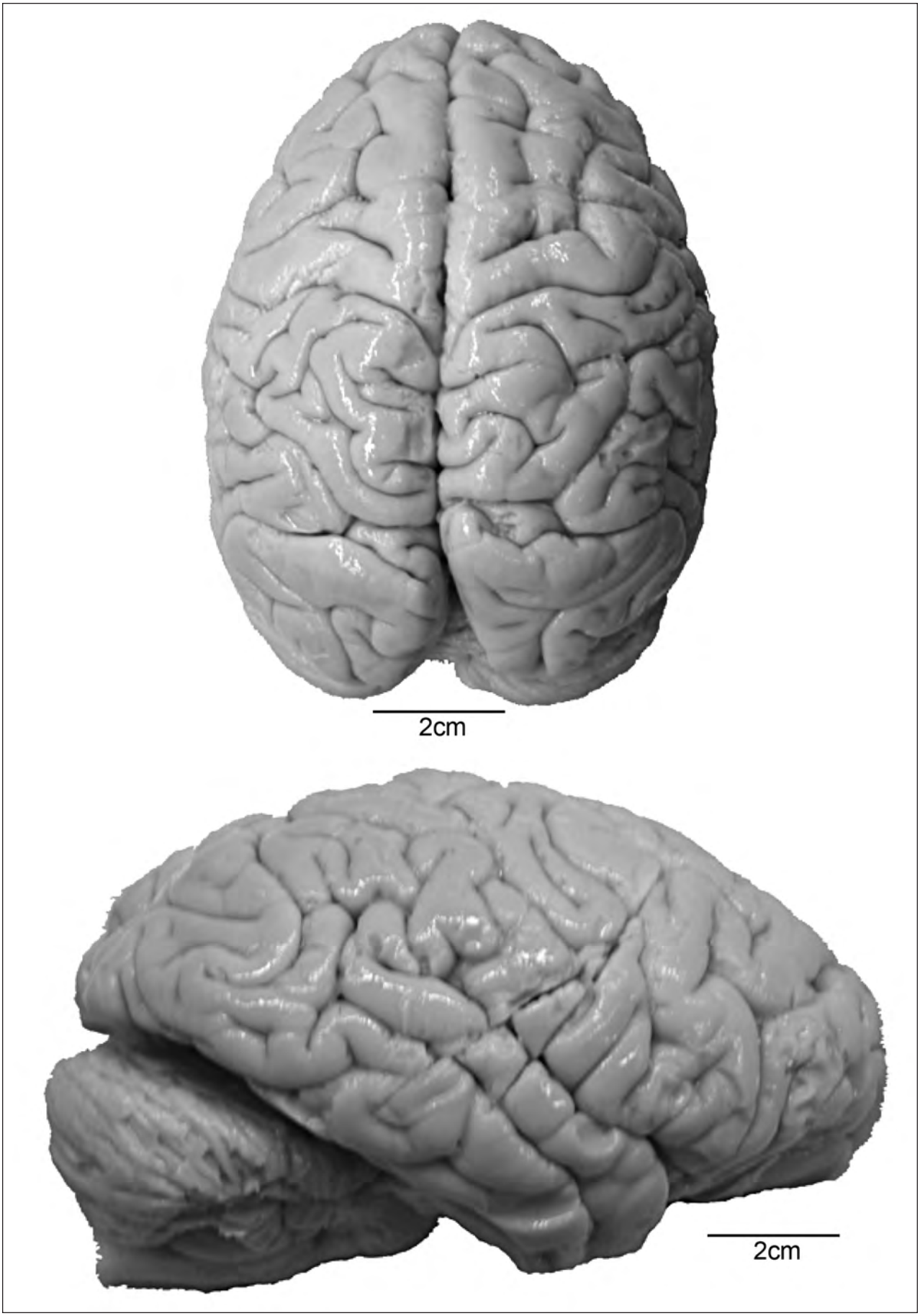
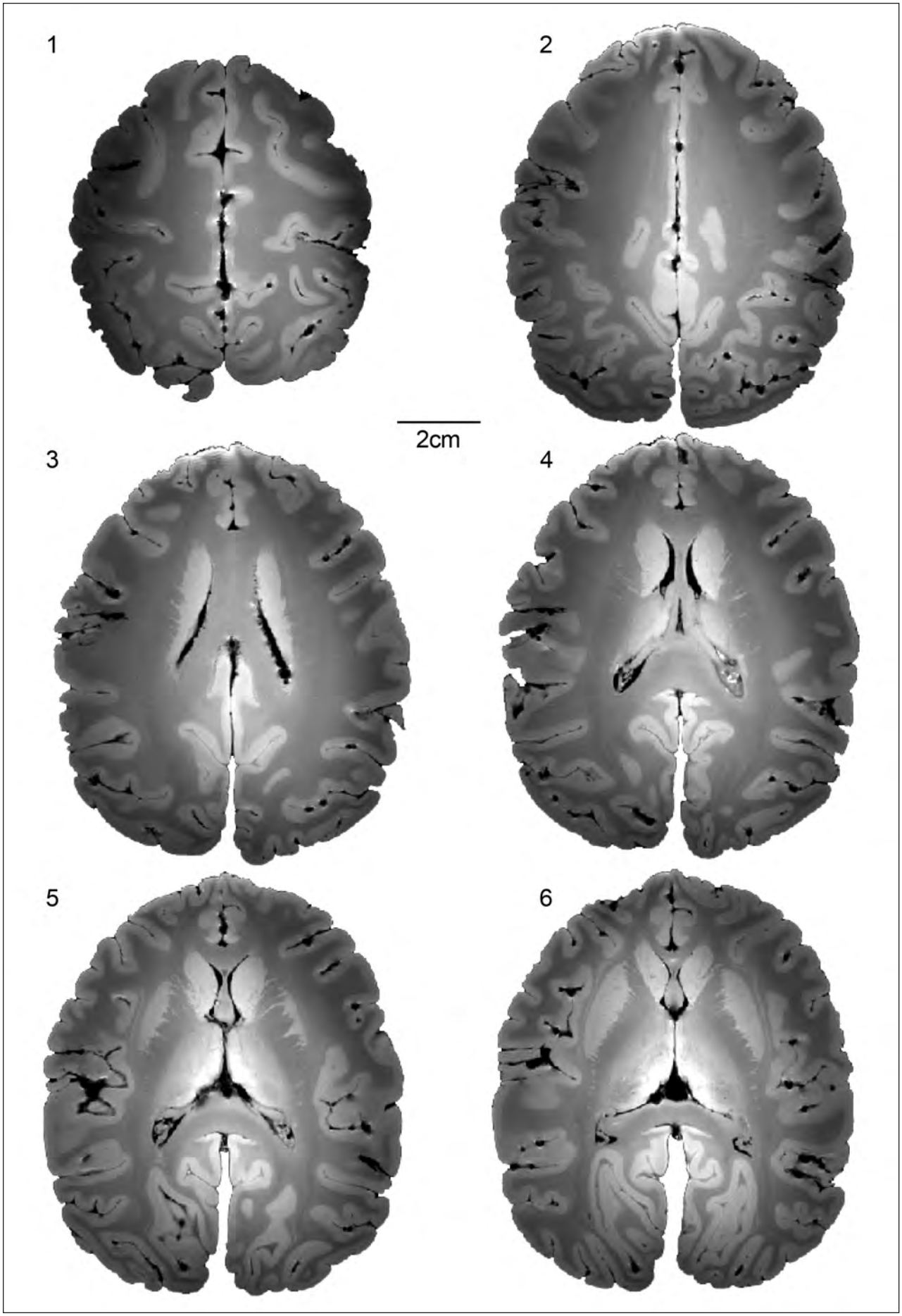


Figure 1. Photographs of the gorilla brain used in this experiment. Top: dorsal view. Bottom: right lateral view.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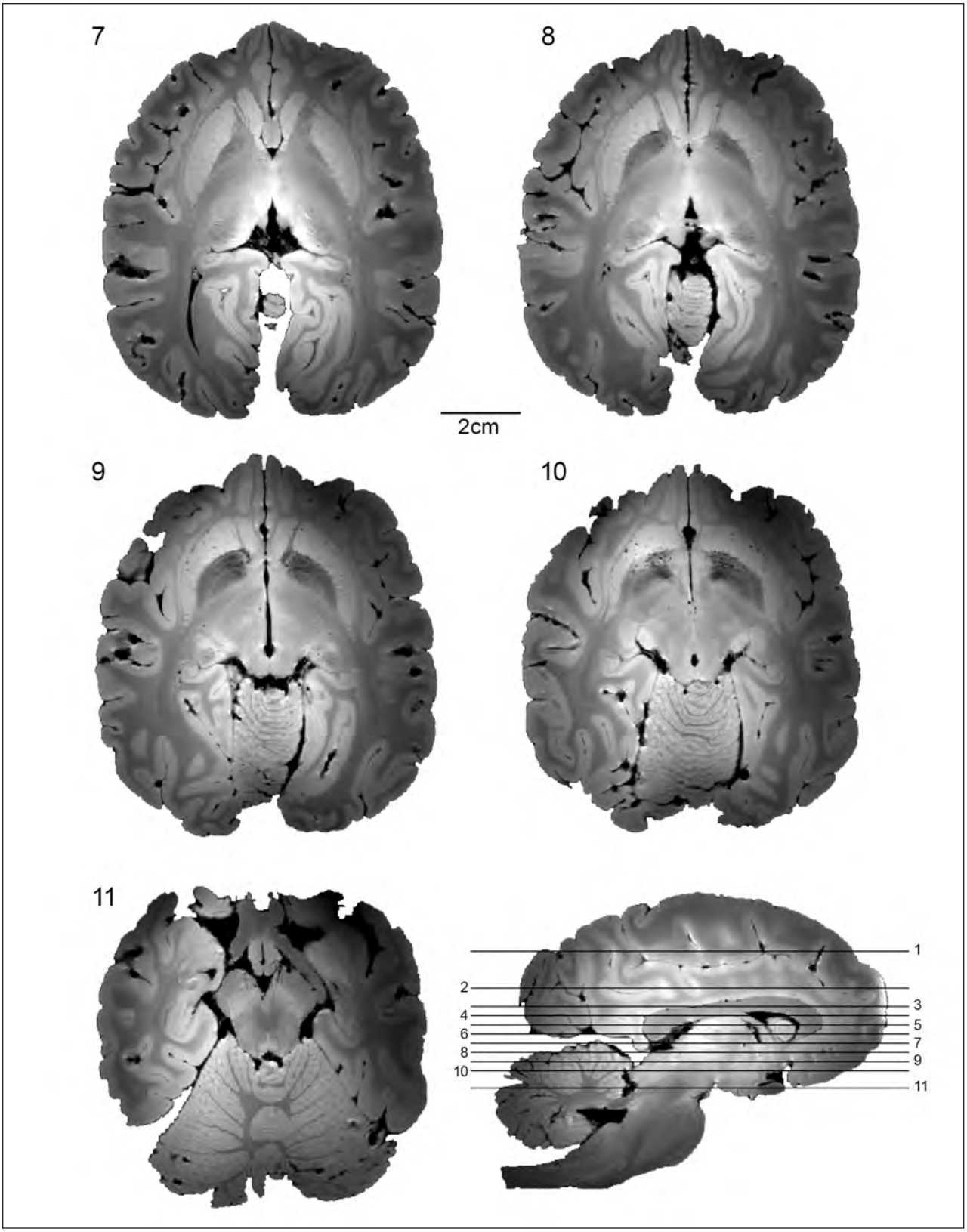

Figure 2. Axial slices through the structural MR image (resolution = 250μm isotropic). Legend in lower right depicts the position of individual slices.

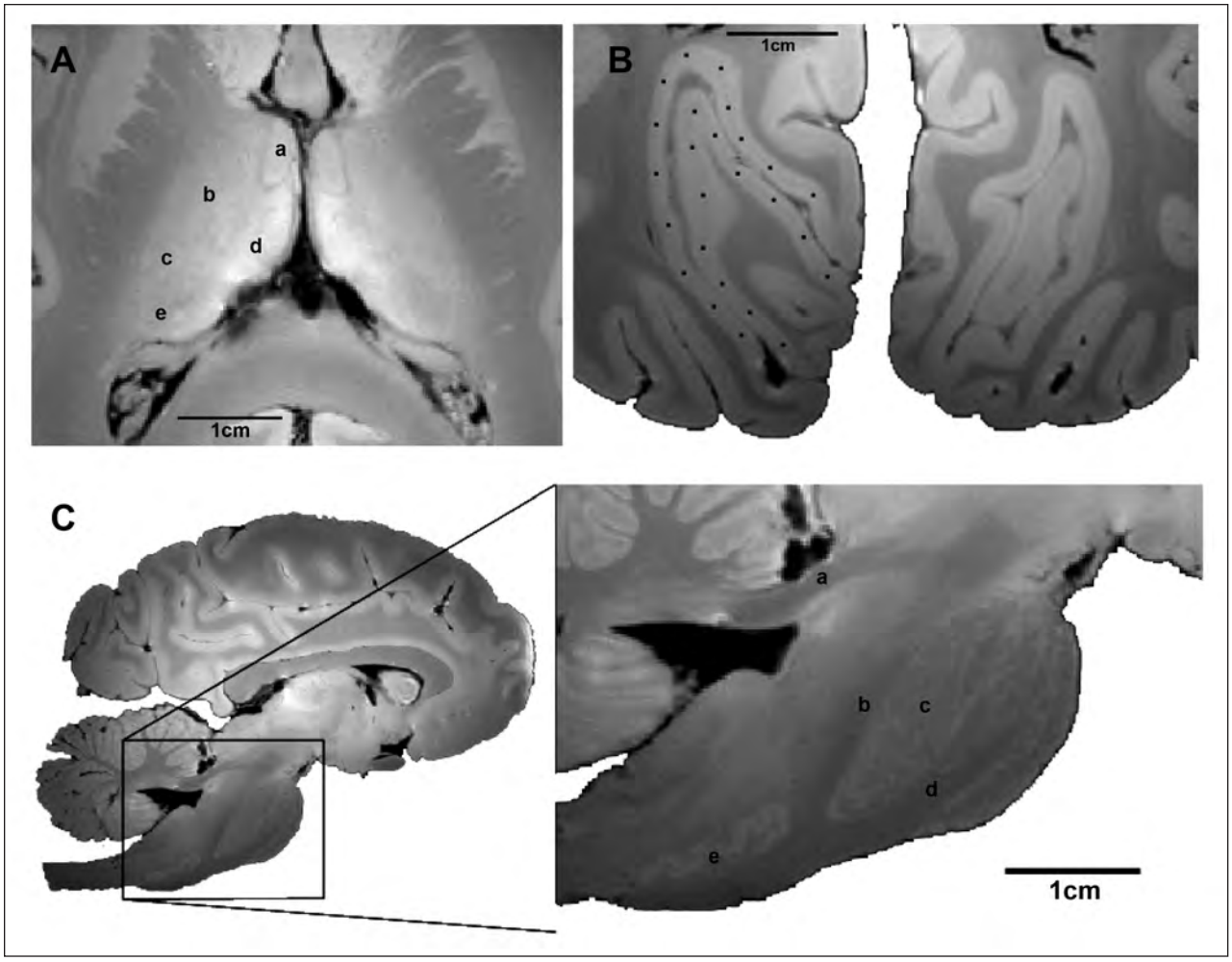

Figure 3. Close-up views of anatomical details evident in the structural MR image. A: Individual nuclei are visible in the thalamus (a: anterior nucleus; b: lateral anterior nucleus; c: lateral posterior nucleus; d: dorsomedial nucleus; e: pulvinar). B: In primary visual cortex, the Stria of Gennari is visible (indicated on the left side by black squares). C: In the brainstem, several anatomical features are evident, including a: the superior cerebellar peduncle; b: the medial lemniscus, c: crossing fibers of the pons, d: the descending pyramidal tract, and e: the inferior olivary nucleus.

Results

The 3D FLASH structural scan yielded excellent anatomical imaging with a resolution of (Figure 2). Minor artifacts such as "ringing" occurred at the extreme edges of the field-of-view, or coincided with small bubbles trapped within cortical convolutions. Notwithstanding these small artifacts, the 9.4 Tesla imaging system produced anatomical scans with 4-6 times the resolution of most large-brain structural MRI experiments (1.5 Tesla clinical imaging systems usually yield a resolution of approximately 1mm).

Several anatomical structures are noteworthy as they are not normally visible on large-brain MR images (Figure 3). Subdivisions of the thalamus are visible, often with clear delineations of thalamic nuclei, such as the internal medullary laminae separating the anterior thalamic nucleus from the lateral-anterior and dorsomedial nuclei (Figure 3a). In the occipital cortex, many image slices display Stria of Gennari, a cytoarchitectural feature delineating the boundaries of primary visual cortex (Figure 3b). And many features are visible in the brainstem, including the clearly undulating surface of the inferior olivary nucleus (Figure 3c).

The high-field system produced equally impressive results for the diffusion imaging sequences. The final voxel size for the DW-MRI volume was 1mm isotropic with an angular sampling of 72 spatial directions. Figure 4 illustrates a subset of the data on the principle-diffusion-direction, which is represented both as vector fields as well as red-green-blue color-coding. FSL is able to model multiple-fiber orientations; we chose a two-fiber model as illustrated in Figure 4c.

Tractography experiments using the two-fiber model produced generally good reproductions of known fiber pathways, but not without some errors (usually caused by the tendency for tract-tracing to "jump" onto adjacent tracts). The first experiment, in which a seed mask was placed around the right lateral geniculate nucleus, yielded a very good representation of the retino-

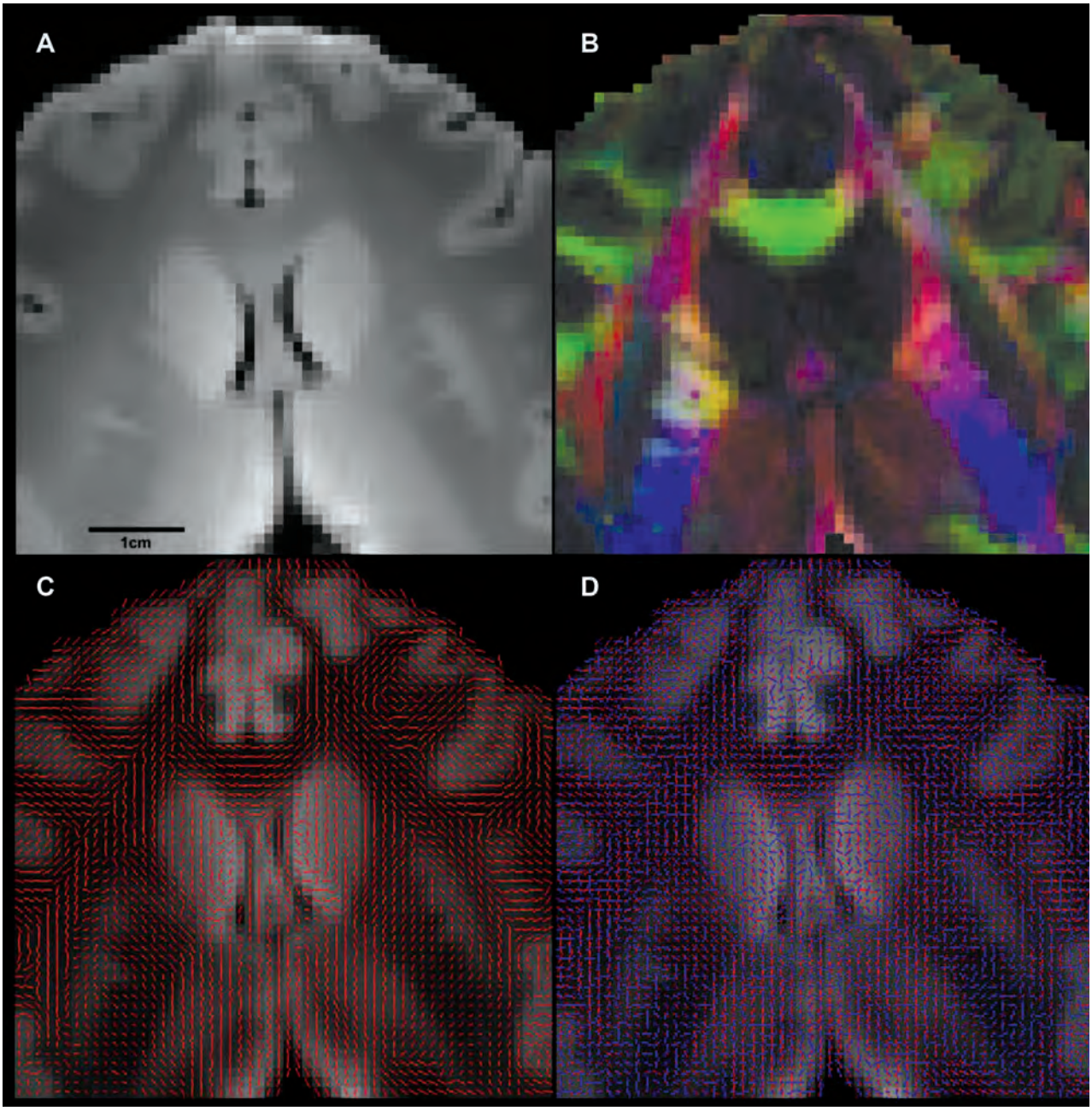

Figure 4. Representation of raw diffusion data (resolution = 1mm isotropic). A: Structural image resampled to 1mm voxel size. B: Red-Green-Blue pseudo-color image representing fiber orientation with each voxel. Voxels labeled green contain fibers oriented axially; voxels labeled red contain fibers oriented longitudinally; and voxels labeled blue contain fibers oriented dorso-ventrally. C. Representation of fiber orientation by vector mapping. Red lines depict the principle diffusion direction. D. The two-fiber model allows identification of regions containing crossing fibers. Red lines depict the principle diffusion direction, while blue lines indicate the minor diffusion direction (i.e., red lines correspond to the first eigenvector of the diffusion tensor and blue lines correspond to the second eigenvector of the diffusion tensor).

geniculo-striate pathway (Figure 5a), but not without errors. The pathway was traced anteriorly through the optic tract and arrived at the optic chiasm. Within the chiasm itself, a tract-jumping error is evident in which the algorithm traces a U-turn to join the optic tract on the opposite side. While this is a reasonable connection through the vector dataset, it is not anatomically correct.

Caudally from the LGN, the algorithm traces the optic radiation and terminates within cortical areas corresponding to the occipital pole and lateral-occipital areas (Figure 5a). However, the algorithm fails to find a pathway to the medial striate cortex. Additionally, the inclusion of connections with lateral occipital cortex anterior to V1 likely represents a "tract-jumping" error involving adjacent V2 projections that also travel through the optic radiation.

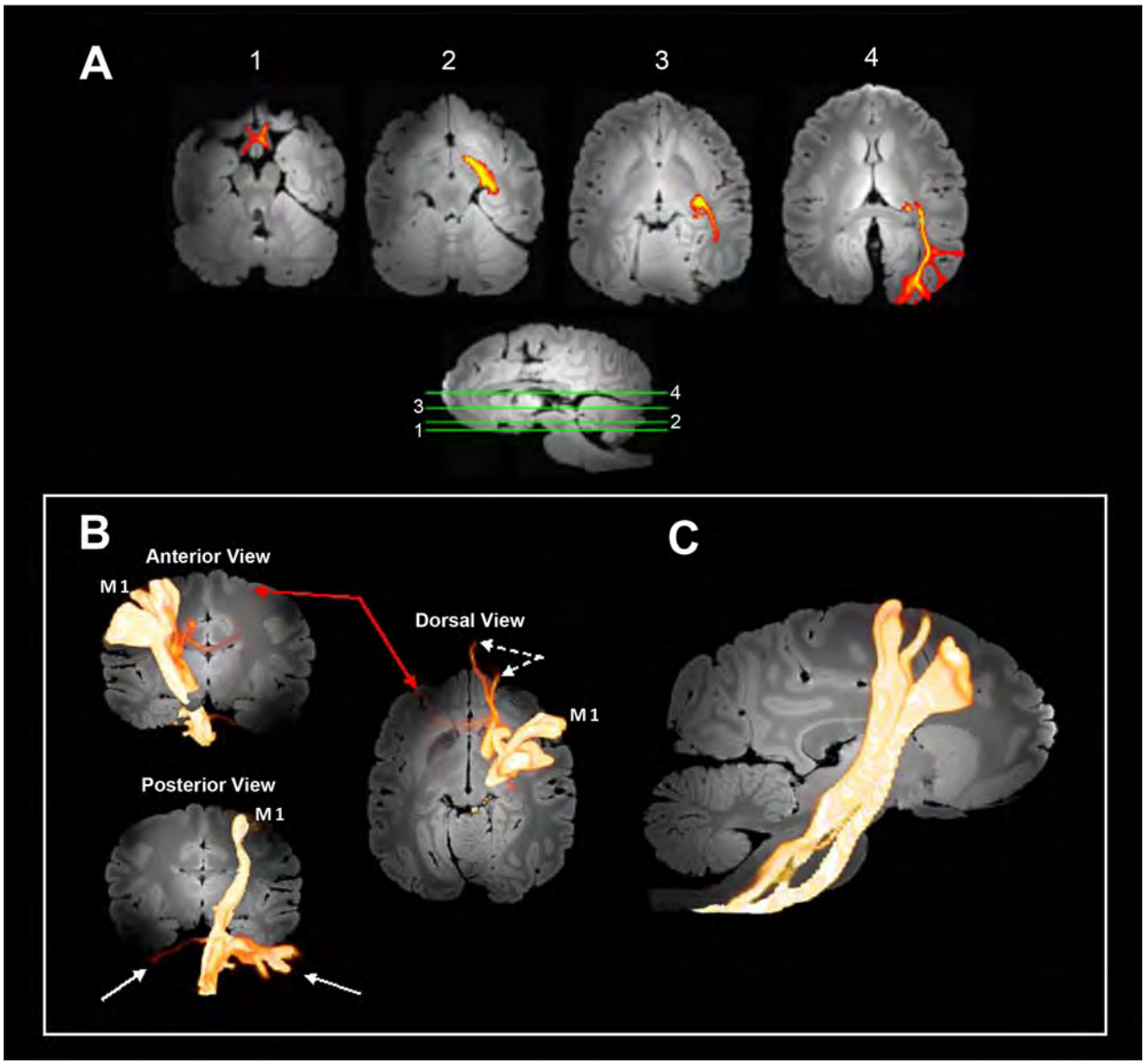

Figure 5. Results of pathway reconstructions by means of probabilistic tractography. A: Tractography of the retino-geniculo-striate pathway reconstructed by seeding in the lateral geniculate nucleus. Bright orange represents pathways of higher-probability. The algorithm successfully reconstructs the visual pathway in both the anterior and posterior direction, but does not reach the medial striate cortex. B: Three-dimensional rendering of the motor pathway reconstructed by seeding from M1 and passing through the posterior limb of the internal capsule. Red arrows point to fibers projecting to the contralateral forebrain. Dashed white arrows point to ipsilateral projections to the forebrain. Solid white arrows point to cerebellar projections. D: Three-dimensional rendering of the corticospinal tract reconstructed by seeding from M1 and including waypoint masks at the posterior limb of the internal capsule and the medullary pyramids. False-positive tracts of the medial and lateral lemniscus and central tegmental tract are visible posterior to the true fibers of the corticospinal tract descending through the pons.

The second tractography experiment on the corticospinal tract also yielded generally good results (Figure 5b). Tractography from the M1 seed mask (with the internal capsule waypoint mask) traced fibers gathering into the posterior limb of the internal capsule and descending through the cerebral peduncles. The tractography algorithm generates terminations in the cerebellum (including a small projection to the contralateral cerebellum) and the medullary pyramids. However, at the level of the ventral thalamus, the algorithm "jumps tracts" and follows thalamic projections to the dorsal prefrontal cortex, including a projection which crosses the corpus callosum and terminates in the contralateral dorsolateral prefrontal cortex. And again, at approximately the level of the red nucleus the tractography bifurcates to include not only the corticospinal tract but also the medial- and lateral-lemniscus, and the central tegmental tract. These latter tracts are false positives (the medial lemniscus car-

ries somatosensory fibers, while the lateral lemniscus and central tegmental tract connect brainstem nuclei with the mesencephalon). Again, it is likely that these errors arise from "tract jumping".

When the medullary pyramids are used as waypoint masks, the cerebellar and frontal connections are discarded, leaving the descending corticospinal tract but still including the false positives: medial- and lateral-lemniscus and central tegmental tract (Figure 5c).

Discussion

Our application of high-field MR imaging to an isolated *ex vivo* gorilla brain produced excellent structural imaging with remarkably high anatomic clarity. The raw diffusion data also appeared to be of excellent quality, with more than twice the resolution normally seen in DTI studies. We performed two sets of trial tractography experiments on known cerebral pathways to test the reliability of probabilistic tractography: the first experiment was intended to trace the retino-geniculo-striate pathway while the second experiment was intended to trace the corticospinal tract. The application of probabilistic tractography to these pathways produced mixed results: the intended pathway was always reconstructed, but additional false-positive pathways were also produced.

The corticospinal tract, in particular, is difficult to reconstruct because it is long and there are many opportunities for errors involving crossing fibers or "kissing fibers" to produce "tract-jumping" false-positives (Holodny et al., 2005). Studies in which the corticospinal tract is successfully isolated from the corticobulbar or other adjacent tracts must use multiple levels of waypoint masks and exclusion masks (Aoki et al., 2005; Reich et al., 2006), or concentrate only on certain levels of the corticospinal tract (e.g. brainstem (Chen et al., 2007)).

The false positives identified during our reconstructions of the retino-geniculo-striate pathway and the corticospinal pathway all occur at areas where the "true" fiber tract (the one we intend to trace) lies adjacent to an unrelated pathway with much the same orientation (a situation termed "kissing fibers"). The result is "tract jumping", and clearly it is important that investigators are vigilant for these errors (Dauguet et al., 2007). The tractography model must be progressively refined (using exclusion masks) to weed out unwanted pathways. When available, the combined use of DW-MRI and fMRI can improve reconstruction results (Guye et al., 2003; Kamada et al., 2005; Staempfli et al., 2008).

Methods for analyzing connectivity from fMRI data (Bartels and Zeki, 2005; Logothetis et al., 1999) are currently impractical for large primates, and there are no reliable long-distance post-mortem neuronal tracers. Robust, quantitative data on global brain connectivity are therefore sparse for humans, and do not exist at all for the apes. DW-MRI fills an important technical gap in our ability to measure human and ape brain connectivity, but it is not without error and must be applied with progressive refinement. As with any method, diffusion tractography has both advantages and disadvantages. Although DW-MRI does not have the high degree of spatial resolution that chemical neuronal tracers can provide it does have the advantage of providing connectivity data for the brain as a whole, which would be impossible to achieve using chemical tracers. At the same time, the application of probabilistic tractography shown here demonstrates that prior knowledge about the position of fiber bundles is essential for weeding out tracts that are false positives.

Conclusions

High-field MR imaging yielded excellent structural and diffusion data even for a fixed, isolated brain. The application of probabilistic tractography to the diffusion data produced mixed results: in both trial experiments the intended pathways were reconstructed, along with false-positive pathways. Prior knowledge of the fiber tracts was necessary to eliminate "tract jumping" errors. DW-MRI fills an important methodological gap for measuring brain connectivity, but future refinement of tractography algorithms will be important for accurate analysis of diffusion data.

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